REMARKS

Claims 1-11 and 49-54 are pending and are the subject of the present office action. Claims 1 and 7 have been amended, and these amendments are illustrated on the attached sheet entitled "Marked Up Version to Show Changes Made". A clean copy of now pending claims 1-11 and 49-54 is provided above.

Each of the rejections set forth in the office action is addressed below.

Section 112 Rejections

Claims 1-5 and 7-11 were rejected under Section 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

Claim 1 was rejected as not providing the "metes and bounds of what an Apo-2 ligand is." Claim 7 was also rejected by the Examiner on the asserted grounds that it is not clear what biological activity is referred to and what is encompassed by the term "variant". Although Applicants respectfully disagree on the basis that the specification provides clear and adequate definitions of each of the terms "Apo-2 ligand", "biological activity" and "Apo-2 ligand variant" (see, e.g, application at pages 12, 13, and 17), claims 1 and 7 have been amended to clarify the language of claims 1 and 7 in view of the definitions provided. The amendments are accordingly not believed to narrow the scope of the claimed invention.

Claims 1, 5-11, and 49-54 were rejected under Section 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The present application clearly provides guidance to those skilled in the art as to what is contemplated as a "divalent metal ion" for use in the disclosed methods and formulations (see, e.g., page 14, lines 27-33 - page 15, lines 1-10). The application further provides ample guidance as to how the claimed formulations may be made and used. That the Examples section of the application does not

provide a working example of each and every divalent metal ion contemplated is not fatal to the issue of enablement. Enablement under Section 112 is not solely determined on the basis of whether working examples are recited in a specification. It is submitted that the application as a whole provides sufficient description to those skilled in the art of protein formulation technology for making and using the claimed formulations of Apo-2 ligand without undue experimentation.

The application likewise provides ample guidance regarding fragments or variants of Apo-2 ligand polypeptide which may be assayed for either apoptosis activity or binding to Apo-2 ligand receptor. The application provides various examples of variants and fragments (e.g., Table I, pages 24 and 25). Moreover, Apo-2L fragments or variants may be assayed for the recited functional properties using assays described in the application itself. As such, there is no undue experimentation for the skilled artisan to formulate such Apo-2 ligand fragment or variant according to the invention.

Withdrawal of the Section 112 rejections is thereby requested.

Section 102 Rejections

Claims 1-11 and 49-54 were rejected under Section 102(b) as being anticipated by Wiley. Applicant respectfully disagrees and submits that the teachings of Wiley fail to anticipate the presented claims.

Page 680 of the Wiley reference contains a single paragraph entitled "Purification of Soluble TRAIL", reproduced below:

> Supernatants from CV1/EBNA cells were harvested 3 days after transfection with pDC409-Flag-TRAIL. These were applied to a column containing the M2 anti-Flag antibody (Hopp et al., 1988), immobilized to a solid support, and washed with PBS. Fractions (800 ml) were **eluted with 50 mM citrate and immediately neutralized in 0.45 ml 1M Tris (pH 8). Fractions were adjusted to 10% glycerol** and stored at -20 C until needed. (emphasis added)

The Examiner asserts that such disclosure anticipates the presented claims. For at least the reasons below, Applicants believe that Wiley neither teaches all the limitations of the claims nor provides an enabling disclosure for the claimed invention.

It is clear from the cited text above that Wiley, at most, describes a preparation of TRAIL protein contained in 50 mM citrate, neutralized in 1M Tris and adjusted to 10% glycerol. This description falls significantly short of teaching the claimed formulations. First, the reference merely states "50 mM citrate" - Wiley is <u>silent</u> about the particulars or source of such citrate. The Examiner's comments regarding aspects of Na citrate and commercial sources of Na citrate therefore appear to be an improper attempt to "read into" this reference information that is not being taught by Wiley.

The Examiner also admits in the office action that "Wiley is silent as to the amount of protein in the eluate, so the molar ratio of Apo-2L versus the divalent ion cannot be determined." (office action at page 5, line 21 - page 6, line 1)

Accordingly, the reference itself does not provide disclosure or teaching of all recited limitations in the claims, and such deficiencies cannot be cured by speculation of exactly what components or how much protein may or may not have been present in the eluate referred to in Wiley. Those skilled in the art would clearly not be able to fill in these "gaps" left by the Wiley reference.

The present application provides for the "the inclusion of one or more divalent metal ions in methods or processes for making Apo-2 ligand, or formulations containing Apo-2 ligand..." (specification at page 7, lines 29-33). Thus, the invention is directed to the "inclusion" or "addition" of one or more divalent metal ions in such methods, processes or formulations of Apo-2 ligand to achieve desired effects. It is respectfully submitted that Example 5 provides an analysis of the metal content of buffers used in the Apo-2L preparation and does not suggest, contrary to the Examiner's assertion, that zinc or cobalt is "inherent" to an Apo-2L formulation.

For all these reasons, Wiley is not an effective 102 prior art

reference and does not anticipate the present claims. It is requested that the Section 102(b) rejection of the claims be withdrawn.

Respectfully submitted,
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MARKED UP VERSION TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (Amended) A formulation comprising Apo-2 ligand and one or more divalent metal ions consisting of the group zinc, cobalt, nickel, cadmium, magnesium, and manganese, wherein the concentration of said one or more divalent metal ions present in the formulation is at a <2X molar ratio to said Apo-2 ligand and the Apo-2 ligand comprises a polypeptide selected from the group consisting of:

(a) a polypeptide having amino acid residues 1 to 281 of Figure 1 (SEQ ID NO:1);

(b) a polypeptide having amino acid residues 114 to 281 of Figure 1 (SEQ ID NO:1);

(c) a fragment of the polypeptide of (a) or (b) which induces apoptosis in at least one type of mammalian cell or binds an Apo-2 ligand receptor; and

(d) a polypeptide having at least 80% identity to the polypeptide of (a) or (b), and induces apoptosis in at least one type of mammalian cell or binds an Apo-2 ligand receptor.

Claim 7 has been amended as follows:

7. (Amended) The formulation of claim 1 wherein said Apo-2 ligand comprises amino acids 1 to 281 of Figure 1 (SEQ ID NO:1) [or a biologically active fragment or variant thereof].